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(54) Carrier material for administration of drugs.

(57) The invention concerns a readily dissolvable carrier material having sufficient rigidity for administration of drugs, nutrients, vitamins, biologically-active materials, foodstuffs and combinations thereof. This carrier material is capable of rapid dissolution by saliva, bodily fluids or other liquid comprising an interim skeletal structure of a water-soluble, hydratable gel or foam forming material, preferably a proteinaceous material, such as with maltodextran, in the hydrated state and dehydrated to leave spaces in place of hydration water. On dissolution by saliva, bodily fluids or other liquids the composition becomes a liquid system.

Further, the invention concerns a method for manufacturing this material using a desiccation step.

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**CARRIER MATERIAL FOR ADMINISTRATION OF DRUGS AND THE LIKE AND METHOD OF MANUFACTURING SUCH CARRIER MATERIAL**

The present invention is directed to a readily dissolvable carrier material for administration of drugs, nutrients, vitamins, biologically-active materials, foodstuffs, and any other medically useful materials or materials capable of sustaining human or animal life, and combinations thereof and to a method of manufacturing such carrier material. This carrier material may be a semi-rigid or rigid solid carrier having a high degree of void space for carrying the drugs, nutrients and the like. The carrier material of the present invention is intended to be capable of relatively immediate dissolution into liquid form upon contact with animal or human saliva or water for oral ingestion.

In specific embodiments, carrier materials of the present invention are dissolvable and/or dispersible in aqueous liquids for liquid administration of drugs, nutrients and the like. In any embodiment, the compositions of the present invention are promptly available for absorption by mammals and can be prepared in the form of wafers, tablets, granules, powders or in liquid form for administration to man and animals. In particular, the methods and compositions of the present invention are directed to a new freeze drying process to dehydrate foodstuffs or hydrated gel and foam materials, particularly proteinaceous substances, thereby leaving porous solid materials capable of absorbing and adsorbing high percentages of the drugs, nutrients, and the like, and capable of rapid dissolution in aqueous liquids or in the mouth of man and animals for prompt delivery of active materials to the bloodstream.

The method and compositions of the present invention are directed to an alternative method of drying drug and nutrient carriers or nutrients that produce solid, rigid, but rapidly dissolvable drug and nutrient carriers or nutrients capable of rapid liberation of the active component to the body in a method that yields new and unexpected results over extant methods of freeze drying.

Accordingly, it is an objective of the present invention to provide a new and improved composition comprising a porous, dehydrated solid carrier for drugs, biologically-active materials, nutrients, and the like that dissolves unexpectedly quickly in water or in the mouth of the recipient for unexpectedly fast delivery of an active substance to the bloodstream.

Another objective of the present invention is to provide a new and improved method of dehydrating a gel or foam solid material in gel or foam form such that the gel or foam substantially retains its gel led or foamed volume, and retains sufficient

rigidity for handling and oral ingestion, but loses most or all of its water content to provide a solid, skeletal carrier that is exceptionally porous, capable of carrying many times its weight in a liquid active substance and capable of unexpectedly quick dissolution when orally ingested.

A still further objective of the present invention is to provide a method of manufacturing such a composition or dried foodstuff and/or drug without needing a lyophilization or other vacuum step.

The compositions of the present invention have several advantages over conventional oral dosage forms:

(1) the described formulations overcome objectionable tastes of incorporated nutrients and drugs;

(2) as compositions of this invention disintegrate in the mouth or when, as an option, the formulations are prepared and taken in liquid form, such as suspensions, the compositions retain the

characteristics of a stable suspension; and  
(3) the medical and nutrient components of the compositions are quickly available for absorption by the body.

Finished products of this invention are ideal for persons who have difficulty ingesting drugs, biologically-active materials and nutrients which are commonly prepared as pills or tablets.

In accordance with an important embodiment of the present invention, a composition of (1) a hydrogel or foamed, non-toxic, edible solid carrier material, such as a proteinaceous material, particularly gelatin or a gelatin derivative, e.g., gelatin; gelatin A; gelatin B; modified fluid gelatin; albumin;

gelatin A, gelatin B, modified fluid gelatin, albumin, and the like; or hydrogels formed from materials such as acacia, tragaganth, and/or guar gum; or aqueous foams formed with any anionic, cationic or amphoteric surfactant, either synthetic or natural (biosurfactants) e.g., lecithin; together with (2) a non-toxic, edible, mono-, di- or polysaccharide, capable of rigidifying the hydrogel or foam substance during dehydration thereof, for example dextrose or

During dehydration thereof, for example, dextran or a dextran derivative, such as maltodextran, can be dried in accordance with the present invention to leave a porous skeleton carrier, preferably of a proteinaceous material, capable of absorbing and/or adsorbing many times its weight in a drug and/or nutrient and the like.

In a preferred form of manufacturing, the solid, porous, skeletal carrier is formed by drying the fully hydrated gel or foam material from the gel or foamed state by transfer of water from the hydrated material to an alcohol solution, when both the hydrated gel or foam material and the alcohol

are frozen or near freezing, without necessitating vacuum conditions, as needed for lyophilization.

A literature search of Chemical Abstracts 1975 to 1988 failed to reveal any reference which anticipates or suggests the water removal methods of this invention or the products produced by such methods.

Reference texts such as Remington's Pharmaceutical Sciences, 15th Edition, 1976, and Lachman et al., The Theory And Practice Of Industrial Pharmacy, Lea & Febiger, 1978, describe the process of lyophilization as a method to stabilize water and heat-sensitive drugs.

Patent references which include lyophilization in their respective methods are exemplified by Alexander U.S. Patent No. 4,573,883; Lafon U.S. Patent No. 4,616,047; Vendel U.S. Patent No. 3,496,267; and Saferstein, et al. U.S. Patent No. 4,752,466. In each of these patents a method involving lyophilization or freeze drying under vacuum conditions of unstable compositions is disclosed.

Aside from the common use of low temperature, the low temperature drying method of the present invention has very little similarity to the process of lyophilization. The differences of method and product between this invention and the well known lyophilization process will become more apparent hereinafter.

Lyophilization involves the use of mechanical equipment and control of vapor pressure to produce stabilized drugs. In contrast, the method of the present invention includes the use of an organic solvent and is based on the chemical process of solubilization and dissolution to produce drug and nutrient delivery compositions, preferably under ambient pressure conditions.

In brief, the present invention is directed to compositions and methods providing porous, semi-rigid or rigid solids and semi-solids that disintegrate virtually instantaneously when contacted by water, saliva, and aqueous solutions and dispersions and are particularly useful for the oral delivery and ingestion of drugs, nutrients and the like. As used in this disclosure, the term "drug" means any composition defined as a drug, e.g. by "Dorland's Medical Dictionary, 27th Ed., 1988, W.B. Saunders Company, Philadelphia, U.S.A., etc. Also, the terms "nutrients", "foods" and "foodstuffs" are used interchangeably and mean any composition in liquid, solid or semi-solid form, without limit, or combinations thereof that are ingested and assimilated by an animal, particularly man, to maintain growth and life. These compositions which may be used singly or in any combination in conjunction with the disclosed delivery system include vitamins, minerals, essential and non-essential amino acids, cations, anions; and also

5 fats, proteins and carbohydrates, without limit, including nutritive derivatives therefrom. For purposes of this specification, powdered, granular or other forms of beverages such as coffee, milk and the like are included as "food" compositions that can be prepared by the method of the present invention.

10 Finished products of this method may be in the form of wafers, tablets, powders, granules or liquid forms. Alternatively, finished products of the present invention in the form of wafers, powders or granules may be used to prepare emulsions and suspensions of drug, biologically-active, medical or nutrient components.

15 The methods of the present invention may also produce useful freeze dried compositions of food and drug compositions that are more stable, and more capable of dissolution and dispersion than those produced by other methods.

20 In an important embodiment of the present invention, a composition of (1) a hydrated gel or foam material and (2) a rigidifying agent for the gel or foam, is intimately contacted with an anhydrous organic liquid desiccant, such as anhydrous ethyl alcohol at a temperature of about 0 °C or below, until substantially all of the water is removed from the gel or foam material. To achieve the full advantage of the present invention, a homogenous mixture of the gel or foam, together with a rigidifying agent for the gel or foam is immersed in the liquid desiccant until completely dehydrated.

25 Preferably, the component materials of the compositions are sequentially combined to produce interim products that are subjected to processes of solubilization and dissolution at temperatures of about 0 °C or below; preferably -10 °C or lower. An ice-dissolving anhydrous organic desiccant is used for dehydration in accordance with the preferred process of the present invention. The organic liquid water removal step removes the water from the composition being prepared and provides new and unexpected advantages in the finished products. The finished products in accordance with the method of the present invention are complete when from about 50% to about 100% by weight of the water of the hydrated gel or foam material of this method have been removed and transferred to the liquid desiccant.

30 35 40 45 50 55 The water used to make the hydrated gel can be any water, particularly pure water such as distilled water. It has been found that structured water that has been polarized, particularly the equilibrium phase water and/or coacervate phase water from a two phase coacervate water composition provide increased structural integrity to the solid carrier materials and increase production speed. Equilibrium phase water and coacervate phase water can be obtained by the methods disclosed in Ecanow

U.S. Patent Nos. 4,343,797; 4,588,032; 4,596,788; and preferably Ecanow U.S. Patent No. 4,539,204, which patents are hereby incorporated by reference. Two phase aqueous coacervate compositions having non-miscible water phases (equilibrium phase water and coacervate phase water) in equilibrium due to their differences in polarity are well known, and any non-toxic equilibrium phase water and/or coacervate phase water is suitable in accordance with this embodiment of the present invention. Coacervate phase water is preferred because of its ability to impart increased structural integrity to the solid carriers of the present invention while retaining their porosity and prompt dissolution properties.

In addition to improving the structural integrity of the water composition, i.e. less crumbling during packaging and the like, the use of coacervate phase water as opposed to distilled water to formulate the wafer composition reduces the time necessary to produce the finished product by approximately 10%. Given that anticipated manufacturing runs of the product will be 50,000 wafers or more per week, the savings in processing time is believed to be significant.

In this method, the water-hydrated composition of the gel or foam material and a rigidifying agent therefor are frozen in a vessel suitable for maintaining temperatures of 0°C or lower. The water removal steps may be repeated as often as is required to produce the required degree of dehydration.

To achieve the full advantage of the present invention, the finished compositions are completely dehydrated. On completion of the low temperature desiccant water-removal steps, the resulting product optionally can be further dried by any of the conventional methods to provide porous, solid drug, biological and/or nutrient delivery compositions in the form of wafers, tablets, granules and powders, or dried food or foodstuffs or the like. If desired, the solids can be rehydrated to provide liquid compositions.

Incorporation of a desired dose of the medical or nutritional component(s) in the porous solid carriers of the present invention and, as preferred, the addition of one or more flavoring agents complete the process for manufacturing the carrier material of the present invention. The finished compositions are suitable for oral administration and provide new and unexpected rapid liberation of the active component to the bloodstream of the recipient, particularly for epilingual administration. Since the compositions of the present invention disintegrate instantaneously in the mouth of the user, their contents are promptly available for absorption by the body. The finished products of this invention can be prepared as wafers, tablets, granules, powders,

or as required as liquid forms such as suspensions and can be administered to man and animals. The methods and compositions of the present invention include methods to prepare freeze dried foodstuffs, and produce drug formulations that have improved stability and dispersibility in liquids.

The present invention may specifically provide a new and improved gelatin-polysaccharide solid carrier, and method of manufacturing the solid carrier, for oral administration of active materials, such as drugs, biologicallyactive materials, foods, nutrients, vitamins and the like that is unexpectedly porous for receipt of the active material and is unexpectedly readily dissolvable in the mouth with saliva so that the active material is quickly assimilated through the mouth tissue or ingested into the GI tract.

The present invention may also specifically provide a new and improved method of freeze drying a hydrated, proteinaceous solid carrier material by intimately contacting the carrier, in substantially completely hydrated form, with an anhydrous desiccant, at 0°C or below, to transfer water, in its frozen state, to the desiccant by sublimation or dissolution or solubilization.

The above and other aspects and advantages of the present invention will be better understood in conjunction with the following detailed description of preferred embodiments and their manufacture:

The finished products of the present invention may be wafers, tablets, granules, powders or liquids. Tablets or wafers weighing about 100 to 150 mgs are preferred and may be of any size appropriate for oral administration. The compositions of this method may also be introduced into the body by other routes of administration. The disclosed carrier compositions may range in weight from about 1/2 gram to about 1200 mgs or more. The preferred method comprises the following steps: (1) Mix the following ingredients together: about 1 gram of flavored gelatin powder or other gelatin-based equivalent, about 2 grams of maltodextrose, about 0.5 gram of gelatin A; about 2 grams of sucrose, optionally for palatability, and as preferred, about 1 gram, or other desired dosage, of flavoring agents or sweeteners, such as ASPARTANE®. The quantities may be adjusted as preferred by the formulator. After mixing these components, add coacervate phase water in an amount that will make a final volume of about 100 ml., (2) heat while stirring the product of step (1) to about 60°C or until the product becomes a visually clear solution. Next, (3) cool the product of step 2 to about 37°C or less but preferably short of freezing, (4) following step 3, the required quantity of the nutrient, drug or other active component is dispersed in the product of step 3. As preferred, one or more flavoring agents may be added to the

product of step 3 at the same time the drug component has been mixed into the product of step 3 (5) Next, rinse the molds to be used in forming the composition with any pharmaceutically acceptable coating liquid or lubricant, for example a solution of about 10% of a phospholipid, such as lecithin, in grain alcohol of about 150-190 proof. (6) Allow the molds to dry at ambient temperature. (7) Next, fill each compartment of the mold with that quantity of the product of step 4 as will give the desired unit dose in each finished wafer or tablet as preferred. (8) Store the product of step 7 at a temperature of 0 °C or lower for about 30-60 minutes or until the molded product (e.g. wafer or tablet) is frozen solid. Temperatures of about -20 °C to about -30 °C are preferred. (9) Next, on completion of Step 8, the frozen semi-finished product is removed from the mold.

At the option of the formulator, any one step or combination of process steps 1 through 8 and the related optional steps may be repeated to produce a semi finished product comprised of any number of layers as preferred by the formulator. The frozen tablets are removed from the mold and contacted with a suitable anhydrous alcohol, e.g. ethyl alcohol, such as by immersion therein, preferably in an airtight (hermetically sealed) container, step (10), as follows: The weight ratio of alcohol to the product can be approximately at least 10:1 alcohol to product, but is preferably about 40:1. This ratio may be adjusted as desired by the formulator. Next, place the product of step 8 in a suitable fluid-permeable container, e.g. a plastic container which may be a fine mesh plastic bag or a plastic bottle containing multiple holes of 0.5 mm or less or more and immerse in a container of anhydrous ethyl alcohol maintained at a temperature of -15 °C or lower. The water content of the alcohol can be measured before this step. Step 10 continues until the water content of the alcohol is about 2.5% or more. The process of step 9 is repeated using a fresh supply of anhydrous alcohol until about 100% of the water has been removed from the dosage form formulation. Next, optionally, place the tablets or wafers resulting from step 10 on blotting paper and transfer quickly to a vacuum chamber. (11) Optionally vacuum dry the product of step 10 at ambient temperature until no odor of the ethyl alcohol remains. (12) A desired quantity of the drug component then is added by means of a pipette to the surface of each wafer or tablet after vacuum drying.

Another method is as follows: (1) Mix the following ingredients together: about 1 gram of flavored gelatin powder or other gelatin-based equivalent, about 2 grams of maltodextrose, about 0.5 gram of gelatin A; about 2 grams of sucrose, optionally for palatability, and as preferred, about 1

gram, or other desired dosage, of flavoring agents or sweeteners, such as ASPARTANE®. The quantities may be adjusted as preferred by the formulator. After mixing these components, add distilled water in an amount that will make a final volume of about 100 ml., (2) heat while stirring the product of step 1 to about 60 °C or until the product becomes a visually clear solution. Next, (3) cool the product of step 2 to about 37 °C or less but preferably short of freezing, (4) rinse the molds to be used in forming the tablets of this method with any pharmaceutically acceptable coating liquid or lubricant, for example a solution of about 10% of a phospholipid, such as lecithin, in 190 proof grain alcohol. (5) Allow the molds to dry at ambient temperature.

Next, (6) fill each compartment of the mold with about 1 ml of the product of step 3. (7) Store the product of step 6 at a temperature of 0 °C or lower for about 30 minutes or until the molded product (tablet) is frozen solid. (8) Remove the product of step 7 from storage and add that quantity of the drug, nutrient or combinations of each, preferably in powder or liquid form, e.g., as an aqueous solution, as preferred by the formulator, to the surface of each tablet within the mold. During this step, the product should be protected from thawing. It is preferred that the product of step 8 is further processed with step (9) which comprises the following: remove the product of step 8 from storage and add from about 0.5 to about 3 mls of the product of step 1 to the upper surface of each frozen tablet in the mold. (10) Refrigerate the product of step 9 for about minutes or more at 0 °C or lower. At the conclusion of step 10, if preferred, the product is removed from refrigeration and one or more flavoring agents are added to the surface of each frozen tablet in an amount ranging from a trace amount to one drop or more according to the preference of the formulator. At this point, the product comprises a semi-finished frozen tablet comprising of three layers.

At the option of the formulator, any one step or combination of process steps 1 through 8 and the related optional steps may be repeated to produce a semi finished product comprised of any number of layers as preferred by the formulator. On completion of step 10 the frozen tablets are removed from the mold and contacted with a suitable liquid organic desiccant, e.g. anhydrous ethyl alcohol, such as by immersion therein, preferably in an airtight container, step (11), as follows: The weight ratio of alcohol to the product can be approximately at least 10:1 alcohol to product, but is preferably about 30:1 to about 50:1, e.g. about 40:1. This ratio may be adjusted as desired by the formulator. Next, place the product of step 10 in a suitable plastic container which may be a fine mesh plastic

bag or a plastic bottle containing multiple holes of 0.5 mm or less or more and immerse in a container of anhydrous ethyl alcohol maintained at a temperature of -15 °C or lower. The water content of the alcohol can be measured before this step. Step 11 continues until the water content of the alcohol is about 2.5% to about 5% by weight. The process of step 11 is repeated using a fresh supply of anhydrous alcohol until about 100% of the water has been removed from the dosage form formulation. Next, (12) place the tablets resulting from step 11 on blotting paper and transfer quickly to a vacuum chamber. (13) Vacuum dry the product of step 11 at ambient temperature until no odor of the ethyl alcohol remains.

In another embodiment of the present invention, (14) the desired dose of the drug component is added by means of a pipette to the surface of each tablet after the product has been vacuum dried.

In accordance with another important embodiment of the present invention to produce the porous carrier materials, the hydrated composition of gel or foam material and gel or foam material rigidifying agent preferably in a frozen state, are spread on a preformed sheet. The sheet then is placed in a suitable freezer chest, preferably manufactured of porcelain. A container of anhydrous ethyl alcohol also is placed in the freezer chest in a weight ratio of at least 10:1 alcohol to wet product, e.g., 40:1. The temperature of the interior of the chest is maintained at the temperature ranging from about 0 °C to about -15 °C or lower. The transfer of water from the starting materials to the alcohol is continued until about 90% to about 100% of the solvent is transferred from the starting material to the anhydrous ethyl alcohol. The alcohol is replaced as required to complete the process of water removal. The processed material then is removed from the alcohol and dried by any pharmaceutically acceptable method to remove any alcohol which is present in the composition. The resulting product comprises a porous solid suitable for purposes of oral delivery of drugs, nutrients and the like. The product may be in tablet, powder or granular form, or reconstituted with water or other solvents for a liquid product.

The preferred procedure to add the drug or nutrient component to the porous solid delivery compositions described above is as follows: The component to be added is dissolved in any appropriate solvent including organic solvents. The dissolved drug is added dropwise by means of a hypodermic syringe or other similar device to the surface of the delivery compositions in that amount that will give the desired dose to each product unit. the porous solid, its spaces now containing the drug or nutrient, then is dried using any conven-

5 tional drying method to remove all traces of the solvent used in the formulation step. As preferred, the drug or nutrient component can be added to the interim product during early stages of preparing the porous solids. As preferred by the formulator, any flavoring agent may be added to the product by placing the agent in solution and adding that quantity of the flavoring agent that is preferred to the surface of the product by means by a hypodermic syringe or other similar device.

10 To prepare a granular form of the composition, the finished product is processed with a rotating granulator or other similar grinding equipment.

15 To prepare the powder form of this invention, a fine wire mesh with openings ranging from about 50 to 300 microns is used in place of the blister mold used to form tablets or wafers. The steps described to produce the tablet dosage form then are followed to produce a powder delivery form.

20 The starting materials of this method comprise the following compositions or combinations thereof: any pharmaceutically acceptable gel or foam materials prepared from any surfactant, synthetic or biological, particularly proteinaceous materials such as gelatin, including types A and B fluid gelatin and gelatin derivatives and albumin. Other suitable gel or foam forming compounds of biological or synthetic origin, used singly or in combination, include phospholipids, singly or in combination, particularly lecithin and coacervate egg lecithin.

25 Suitable rigidifying agents for such gels, hydrogels, and foam-forming materials include dextran and dextran derivatives, such as maltodextran; carbohydrates including the mono-, di-, and other polysaccharides. The monosaccharides include without limitation, dextrose, fructose and galactose and the sugar alcohols mannitol, xylitol and sorbitol; the disaccharides include without limitation sucrose, lactose and maltose. Oligosaccharides include polymers of the monosaccharide sugars, polysaccharides include dextrans having molecular weights ranging from 40,000 to 90,000. The amount of rigidifying agent is an amount sufficient to rigidity the gel or foam material, generally about .1 to 5 times the weight of the gel or foam forming material (dry basis).

30 The liquid, anhydrous organic desiccants used for dehydration include any organic solvent without limitation that will dissolve ice at about 0 °C or less, including acetone and the alcohols but especially ethyl alcohol about 150 to 200 proof; about 200 proof is preferred. As preferred, any pharmaceutically acceptable flavoring agent or combinations of such agents, including natural and synthetic flavoring agents, such as ASPARTANE® and flavor enhancing agents, such as the commercial product VELTOL® (Pfizer); preservatives such as methyl paraben, propyl paraben and combinations thereof.

The oral delivery compositions of the present invention are useful to administer drugs in each of the following categories: drugs acting on the central nervous system; drugs acting at synaptic and neuroeffector sites; autacoids, cardiovascular drugs; drugs affecting renal function and electrolyte metabolism; drugs effecting uterine motility; antibiotic drugs; anti-fungal drugs; antineoplastic drugs; drugs acting on blood and blood forming organs and hormones. Nutrients that are useful for oral delivery in accordance with the present invention include water-soluble vitamins, such as the B vitamins and vitamin C; water soluble trace elements such as copper, selenium, calcium, chromium, zinc, magnesium and iron; electrolytes without limitations including sodium, potassium, magnesium, calcium, lithium, ammonium, phosphorous, chloride, iodide, bromide, fluoride, acetate, sulfate, carbonate, phosphate, lactate, gluconate and lactobionate; also carbohydrates; amino acids including leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, arginine, histidine, proline, serine, tyrosine, glycine, taurine and carnitine, as the L-, D- and racemic forms but particularly the L-acids and branched chain amino acids; also keto-analogs of all of the above listed amino acids; partial hydrolysates of proteins and oligo and poly-peptides of synthetic origin; also phospholipids without limitation. As an option, antioxidants, preferably a tocopherol, may be included in formulations of this invention which deliver nutrients.

To prepare freeze dry compositions of food, the following preferred process is used. (1) Freeze a unit of the food composition, e.g., whole milk, at 0°C or below until the unit is converted into a frozen solid. (2) Next, dehydrate the frozen milk in an airtight container using anhydrous alcohol preferably in a weight ratio of alcohol to frozen milk of at least about 10:1 to achieve fast dehydration, as follows: Place the product of step 1 in a suitable fluid-permeable container, e.g. a plastic container which may be a fine mesh plastic bag or a plastic bottle containing multiple holes of 0.5 mm or less and immerse in a container of anhydrous ethyl alcohol maintained at a temperature of about -15°C or below. The water content of the alcohol can be measured before this step. Step 2 continues until the water content of the alcohol is about 2.5% or more. The process of step 2 is repeated using a fresh supply of anhydrous alcohol. The process continues until about 100% of the water (ice) has been removed from the frozen milk. (3) Next, optionally, place the dehydrated frozen milk, e.g., in wafer or tablet form, resulting from step 2 on blotting paper and transfer quickly to a vacuum chamber. (4) Optionally vacuum dry the product of step 3 at ambient temperature until no odor of the

ethyl alcohol remains. Completion of step 4 produces a finished powdered product of freeze dried milk, a dry foodstuff. This product has the flavor of the natural product but has improved stability and an extended shelf life extending to 1 year or more.

To improve the stability and dispersibility of drug formulations, the following process is used. (1) Prepare a slurry of the desired drug using any liquid as the solvent, i.e., water, glycerin, and the like. Water is preferred, particularly coacervate phase water. In the instance of water-insoluble drugs, coacervate phase water or a suspension of the drug in water may be used. (2) Place the composition of step 1 in a suitable fluid-permeable container and follow the procedures of steps 2, 3, and 4 described above with reference to the processing of frozen milk. The finished product comprises the desired drug in powdered form which may be placed in liquid or solid form and administered or stored. If packed under vacuum conditions, the shelf life of the drug may extend to 3 years or more.

## EXAMPLES

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### EXAMPLE 1

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Mix the following ingredients together: 1 gram of flavored gelatin powder, 2 grams of maltodextran, 0.5 gram of gelatin A; 2 grams of sucrose and 1 gram of ASPARTANE®. After mixing these components, add distilled water in an amount that will make a final volume of about 100 ml. Stir and heat the product to 60°C; continue this step until it comprises a clear solution. Next cool the product to 37°C. Prepare blister molds to make the porous tablets by first rinsing the molds with a 10% solution of lecithin in 190 proof grain alcohol. Following the rinsing step, and dry the mold at ambient temperature. Fill each compartment in the mold with 3 mls of the solution described immediately above. Next, store the product at a temperature of -10°C or lower for 40 minutes. Remove the product from storage and add 300 mgs of powdered acetaminophen to the surface of each tablet within the mold. During this step, the product must be protected from thawing. The product is then stored under refrigeration at -10°C for 40 minutes.

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Next, remove the product from storage and add 3 mls of the gelatin-based solution described above to the upper surface of each frozen tablet in the mold. Refrigerate the product for 40 minutes at -10°C.

Transfer the frozen tablets from the mold to a mesh plastic bag. Immerse the bag and its contents in a hermetically sealed container of anhy-

drous ethyl alcohol maintained at a temperature of -20 °C. The immersion step continues until tests reveal that the tablets are completely dehydrated. Replace the alcohol with fresh supplies of anhydrous alcohol as required to facilitate dehydration. Continue this step until no odor or other evidence of alcohol can be detected. On completion of this step, the composition comprises a finished product.

**EXAMPLE**

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Example 2 follows the procedure of Example 1 except that 250 mgs of powdered erythromycin is used in place of acetaminophen.

**EXAMPLE 3**

Example 3 follows the procedure of Example 3 except that ASPARTANE® is not used and the refrigeration temperatures are -20 °C rather than -10 °C.

**EXAMPLE 4**

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Example 4 follows the procedure of Example 1 except that all the formulation steps are repeated prior to the immersing the product in anhydrous ethyl alcohol. The finished product will comprise a six layer tablet.

**EXAMPLE 5**

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The method of Example 1 is followed except that 300 mgs of acetaminophen is mixed into the gelatin based solution after it has cooled. The step of adding acetaminophen to the surface of the frozen inter in product is omitted.

**EXAMPLE 6**

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The method of Example 1 is followed except that 300 mgs of acetaminophen is added to the cooled gelatin-based solution. The finished product of this example contains 600 mgs of acetaminophen.

**EXAMPLE 7**

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The method of Example 1 is followed except that two drops of cherry flavoring is added by pipette to the surface of each formed tablet.

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**EXAMPLE 8**

5 The method of Example 1 is followed except that the finished tablets are processed by a granulator to produce a granular porous solid dosage form.

**EXAMPLE 9**

10 The method of Example 1 is followed except that a fine plastic mesh is used in place of the blister mold. The finished product comprises a powder form of the claimed composition.

**EXAMPLE 10**

15 The method of Example 1 is followed except that the following minerals are added to the cooled gelatin-based solution: iodine 150 mg; calcium, 1 mg; magnesium 400 mg; manganese 3 mg; iron 18 mg; copper 2 mg, zinc 15 mg; and phosphorous, 1 gm. Store the product at 33 °C to give a slurry-like consistency to the product. Following the first freezing step, a composition comprised of 500 mgs of Vitamin C, 15 units of Vitamin E; 15 mg of Vitamin B<sub>1</sub>; 17 mg Vitamin B<sub>2</sub>; 100 mg niacin; 25 mg Vitamin B<sub>5</sub>; 12 mg Vitamin B<sub>12</sub>, and 25 mg pantothenic acid is added to the surface of each semi-finished frozen tablet. The remaining processing steps of Example 1 are used as given. The step in Example 1 in which the drug is added is not used in this Example. In addition, this Example illustrates a method wherein two groups of compositions which are incompatible from a manufacturing point of view can be prepared in a single tablet.

**EXAMPLE 11**

20 The method of Example 1 is followed except that the step in which acetaminophen is added is not used. In this example, 3.5 grams of VIVONEX® (Norwich-Eaton) is mixed into the cooling gelatin based solution and stored under refrigeration at 35 °C to give a slurry-like consistency to the product. The blister molds are filled with 25 mls of this composition.

**EXAMPLE 12**

25 (1) Mix the following ingredients together: about 1 gram of flavored gelatin powder or other gelatin-based equivalent, about 2 grams of mal-

to dextrose, about 0.5 gram of gelatin A; about 2 grams of sucrose, optionally for palatability, and as preferred, about 1 gram, or other desired dosage, of flavoring agents or sweeteners, such as ASPARTANE®. The quantities may be adjusted as preferred by the formulator. After mixing these components, add distilled water in an amount that will make a final volume of about 100 ml., (2) heat while stirring the product of step 1 to about 60 °C or until the product becomes a visually clear solution. Next, (3) cool the product of step 2 to about 37 °C or less but preferably short of freezing, (4) following step 3, 300 mgs of acetaminophen is dispersed in the product of step 3. As preferred, one or more flavoring agents may be added to the product of step 3 at the same time the drug component has been mixed into the product of step 3. (5) Next, rinse the molds to be used in forming the composition with any pharmaceutically acceptable coating liquid or lubricant, for example a solution of about 10% of a phospholipid, such as lecithin, in grain alcohol of about 150-190 proof. (6) Allow the molds to dry at ambient temperature. (7) Next, fill each compartment of the mold with that quantity of the product of step 4 that will give the desired unit dose in each finished wafer or tablet as preferred. (8) Store the product of step 7 at a temperature of 0 °C or lower for about 30-60 minutes or until the molded product (e.g. wafer or tablet) is frozen solid. Temperatures of about -20 °C to about -30 °C are preferred. (9) Next, on completion of step 8, the frozen semi-finished product is removed from the mold.

#### EXAMPLE 13

The method of Example 12 is followed except that equilibrium phase water (in the same amount) from a two-phase coacervate composition is substituted for distilled water.

#### EXAMPLE 14

The method of Example 12 is followed except that coacervate phase water (in the same amount) from a two-phase coacervate composition is substituted for distilled water.

#### Claims

1. A readily dissolvable carrier material having sufficient rigidity for administration of drugs, nutrients, vitamins, biologically-active materials, foodstuffs and the like and combinations thereof capable of rapid dissolution by saliva, water, or aqueous solutions or dispersions, comprising a porous skeletal

structure of a water-soluble, hydratable gel or foam material that has been hydrated with water, rigidified in the hydrated state and dehydrated to leave spaces in place of hydration liquid.

- 5 2. The carrier material of claim 1 wherein the gel or foam material is selected from a proteinaceous material, such as gelatin, gelatin A, gelatin B, fluid gelatin, modified fluid gelatin, gelatin derivatives, albumin or mixtures thereof, or from phospholipids such as coacervate egg lecithin, and lecithin, singly or in combination.
- 10 3. The carrier material of claim 1 or 2 wherein the rigidifying material is selected from the group consisting of a monosaccharide, an oligosaccharide, a polysaccharide, and combinations thereof.
- 15 4. The carrier material of claim 3 wherein the rigidifying material is selected from the group consisting of dextrose, fructose, galactose, mannitol, xylitol, sorbitol, sucrose, lactose, maltose, dextrans, dextran derivatives, and combinations thereof.
- 20 5. The carrier material of claim 4 wherein the rigidifying agent is maltodextran.
- 25 6. The carrier material of claim 5 wherein the maltodextran has a weight average molecular weight of about 40,000 to about 90,000.
- 30 7. The carrier material of anyone of the claims 1 to 6 wherein the hydration water is selected from the group consisting of purified water, coacervate phase water, equilibrium phase water and mixtures thereof.
- 35 8. The carrier material of anyone of the claims 1 to 7 further including a flavoring agent to mask an undesirable taste of the active material upon dissolution in the mouth.
- 40 9. The carrier material of claim 8 wherein the flavoring material comprises ASPARTAN®.
- 45 10. A method of manufacturing the carrier material of anyone of the claims 1 to 9 having sufficient rigidity for carrying and administration of an active material selected from the group consisting of drugs, nutrients, vitamins, biologically-active compounds, foodstuffs, and combinations thereof, comprising the steps of:
  - (a) freezing a solution comprising a water-soluble gel or foam material and a rigidifying agent for said gel or foam material and water, preferably selected from the group consisting of coacervate phase water, equilibrium phase water and mixtures thereof;
  - (b) optionally contacting the frozen material of step (a) with the active material in an amount sufficient to cause the active material to be absorbed or adsorbed within the frozen material without thawing the material;
  - (c) dehydrating the frozen material from step (b) by causing material transfer of water from the frozen material to an organic, liquid desiccant while both the frozen material and the organic
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desiccant are held at a temperature of about 0 °C or below; and

(d) optionally removing the organic desiccant from the dehydrated material resulting from step (c).

11. The method of claim 10 wherein the solution to be frozen according to step (a) contains a quantity of one or more nutrients, drugs, vitamins, biologically-active materials, foodstuffs or combinations thereof.

12. The method of claim 10 or 11 further including adding a flavoring material to the surface of the dehydrated material.

13. The method of anyone of the claims 10 to 12 further including one or more steps of adding a layer of the hydrated composition useful for step (a), in liquid form, onto the surface of the frozen composition resulting from step (a) or step (b), and freezing the layers together.

14. The method of claim 13 including adding an active material to the frozen material resulting from step (a) or step (b) prior to the addition of anyone of the layers of liquid composition and/or after the addition of anyone of the layers of liquid composition.

15. The method of anyone of the claims 10 to 14 wherein the hydrated gel or foam material has been dehydrated in a frozen state by contact with an organic solvent having a freezing point below 0 °C at near freezing temperature.

16. The method of claim 15 wherein the hydrated, frozen gel or foam material is dehydrated by immersing the frozen gel or foam material in a lower alcohol (C<sub>1</sub> to C<sub>5</sub>) at a temperature of 0 °C or below.

17. A method of manufacturing a readily dissolvable, freeze-dried composition of food and/or drug compositions comprising the steps of:

(a) freezing a solution of a water-soluble or solvent-soluble composition or a dispersion comprising foodstuffs and/or drug(s) until the composition is converted into a frozen solid;

(b) dehydrating the frozen material from step (a) by causing material transfer of water from the frozen material to an organic, liquid desiccant while both the frozen material and the organic desiccant are held at a temperature of about 0 °C or below; and

(c) optionally removing the organic desiccant from the dehydrated material resulting from step (b).

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REPORT

EP 90 11 5576

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 084 705 (WYETH) * Claims; page 4, lines 5-26; page 6, lines 22-25; page 7, lines 17-19; page 8, lines 1-2,8-27; page 9, lines 3-8 *	1-8,10,17	A 61 K 9/16 A 61 K 9/18 A 61 K 9/20 A 61 K 47/42
A	FR-A-2 366 835 (WYETH) * Claims; page 2, lines 16-22; page 4, lines 22-25,33-38; page 5, lines 1-2; page 6, lines 17-25 *	1-8, 10-11,17	
-----			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	24 June 91	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

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